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## FEVER ASSESSMENT

### SUMMARY

The onset of fever in the intensive care unit patient must be approached systematically and guided by clinical findings. Current literature emphasizes utilizing a cost-conscious approach, minimizing the use of low yield tests that have little impact on clinical outcome and may be detrimental to the patient.

### RECOMMENDATIONS

- **Level 1**
  - If catheter-related sepsis is suspected, two peripheral blood cultures should be obtained with an additional culture from each indwelling catheter.
  - If a lower respiratory tract infection is suspected, obtain a portable AP chest radiograph.
  - Gram stains of centrifuged urine should be used to select antimicrobial therapy.
- **Level 2**
  - Core body temperature measurements from an intravascular or urinary catheter or esophageal thermistor should be used when available.
  - If clinical evaluation does not strongly suggest a non-infectious cause, blood cultures should be obtained within the first 24 hours of fever.
  - Expressed purulence from an intravascular catheter insertion site should be cultured.
  - Use quantitative catheter cultures to determine the source of bacteremia/fungemia.
  - Do not routinely culture removed intravascular catheters. Culture only those suspected of being the source of infection.
  - Quantitative cultures obtained by either bronchoscopy or catheter lavage should be obtained if pneumonia is suspected.
  - Pleural fluid should be cultured if an adjacent infiltrate is noted or infection is suspected.
  - Evaluation for *C. difficile* infection should begin with a *C. difficile* toxin EIA.
  - Send stool cultures for enteric pathogens or ova and parasite only if diarrhea was present prior to ICU admission, the patient is immunocompromised or it is epidemiologically indicated.
  - Obtain urine for microscopic exam, Gram stain and culture in all high risk patients showing signs or symptoms of UTI.
  - Surgical wounds with suspected infection should be opened to obtain samples for Gram stain and culture. Cultures of the skin overlying a wound should not be performed.
  - If there is sufficient clinical suspicion, a CT scan of the sinuses should be obtained.
  - If CNS infection is suspected, send CSF for Gram stain and culture, glucose, protein, and cell count with differential.
- **Level 3**
  - Chest radiographs, urinalysis, or urine cultures are not indicated in the first 72 hours post-operatively unless history and clinical findings suggest a high probability of infection.
  - Noninfectious causes of fever should be investigated, including new medications and administration of blood products.
  - If fever is accompanied by altered consciousness or focal neurologic deficits, lumbar puncture or evaluation of CSF from an indwelling ventriculostomy should be considered.

### EVIDENCE DEFINITIONS

- **Class I:** Prospective randomized controlled trial.
- **Class II:** Prospective clinical study or retrospective analysis of reliable data. Includes observational, cohort, prevalence, or case control studies.
- **Class III:** Retrospective study. Includes database or registry reviews, large series of case reports, expert opinion.
- **Technology assessment:** A technology study which does not lend itself to classification in the above-mentioned format. Devices are evaluated in terms of their accuracy, reliability, therapeutic potential, or cost effectiveness.

### LEVEL OF RECOMMENDATION DEFINITIONS

- **Level 1:** Convincingly justifiable based on available scientific information alone. Usually based on Class I data or strong Class II evidence if randomized testing is inappropriate. Conversely, low quality or contradictory Class I data may be insufficient to support a Level I recommendation.
- **Level 2:** Reasonably justifiable based on available scientific evidence and strongly supported by expert opinion. Usually supported by Class II data or a preponderance of Class III evidence.
- **Level 3:** Supported by available data, but scientific evidence is lacking. Generally supported by Class III data. Useful for educational purposes and in guiding future clinical research.

## **INTRODUCTION**

Fever is defined as an elevation in core body temperature greater than 38.3°C (101°F) and is one of the most frequently detected abnormal signs in the intensive care unit (ICU) patient population. This physiological response is known to have direct antimicrobial effects, in addition to its role in augmenting humoral and cellular defense mechanisms. Although in some instances fever is indicative of an adequate systemic response, acute onset of fever has been associated with ICU mortality in 12% of cases [1]. Appropriate evaluation of fever, and institution of early, goal directed therapy when indicated, is associated with a clear survival benefit for patients who are septic, experiencing endocrine emergencies, and those with other causes of temperature dysregulation. Fever evaluations in the ICU setting should be guided by clinical assessment instead of automatic laboratory and radiologic tests.

## **LITERATURE REVIEW**

In 2008, the Society of Critical Care Medicine (SCCM) and the Infectious Diseases Society of America convened a task force to update the 1998 practice parameters for the assessment of fever in ICU patients. The 2008 guidelines presented numerous recommendations based on discussion of the published literature and panel members' expertise [2]. The Cochrane Library and the National Clearing House databases were used to identify trials, meta-analyses, literature reviews and most recent clinical recommendations pertaining to the evaluation of the acute onset of fever in the ICU population. Finally, a review of literature published in critical care medicine journals within the last 4 years was conducted and considered in this review.

### **Measuring Temperature**

The first step in evaluating fever is to accurately assess temperature. Although the gold standard for temperature assessment is core temperature obtained in the central circulation, its use is not always indicated in ICU patients. Bladder catheters with thermistors, although costly, have been shown to provide essentially identical readings to thermistors in intravascular sites, are less invasive and provide stable measurements, regardless of urine flow rate [2]. In spite of the fact that esophageal probes have demonstrated temperature monitoring accuracy comparable to that of central venous and bladder catheter thermistors, they are not commonly utilized in the ICU.

Less invasive modes of monitoring core body temperature incorporate the use of infrared thermometry to record temporal artery and tympanic membrane temperatures. Although initially the temporal artery thermometer was considered to be as accurate and precise as invasive core temperature measurements, observational studies have demonstrated a mean difference of -0.44°C when compared to bladder catheter temperatures. Due to the lack of consensus with other established modes of core body temperature monitoring, the use of temporal artery thermometry is not recommended in situations where accurate and precise body temperature monitoring is indicated (Level 2) [3]. Infrared ear thermometry has been shown to yield inaccurate readings in the setting of inflammation of the auditory canal or tympanic membrane as well as poor correlation with core temperature readings.

A study among 110 ICU patients comparing central venous, axillary, tympanic membrane, and urinary bladder thermistors found that tympanic membrane measurements showed only modest correlation with central venous ( $r=0.77$ ), urinary ( $r=0.69$ ), and axillary ( $r=0.76$ ) temperatures. The average difference between central venous and urinary temperature was small at -0.05, with a statistically significant correlation ( $p=0.92$ ). This paper adds to a growing body of evidence that questions tympanic membrane measurements and suggests that urinary bladder temperature monitoring is the preferred alternative when central venous monitoring is not indicated and Foley catheter placement is indicated (Level 2) [4].

### **Evaluation of the Patient**

With new onset of fever, a thorough search for possible etiologies should be performed. It is important, however, to maintain a lower temperature threshold among the immunocompromised population. It should also be considered that infections may be concealed by euthermia or hypothermia in certain patient populations, such as the elderly, those with open abdominal wounds, extensive burns, and those receiving extracorporeal membrane oxygenation or continuous renal replacement therapy [2]. Regardless

of the patient's status it is important to conduct both a careful physical examination and thorough review of the patient's medical record. This should include:

Review of:

- Patient's injuries
- Previous cultures
- Prior antibiotic therapies
- Medications
- Recent chest radiograph (if available)

Examination of:

- Intravascular catheter insertion sites
- Drainage tubes and their output
- Wounds
- Extremities for swelling

### **Infectious vs. Non-infectious Causes of Fever**

The initial goal in fever assessment should be to determine if it is infectious or non-infectious in etiology. Some common non-infectious causes for fever seen in the ICU are listed in Table 1. Many of these are diagnoses of exclusion and many patients will have risk factors for both infectious and non-infectious etiologies. Unless there is strong evidence that the fever is non-infectious in nature, diagnostic evaluation to identify the potential source of infection should be promptly initiated. This approach, however, will vary when assessing the febrile postoperative ICU patient. In patients with fever within 72 hour of surgery, no additional laboratory, culture, or radiographic evaluation is necessary unless directed by clinical findings, suspicion for aspiration or a compromise of sterile technique [2,5]. Serum procalcitonin levels and endotoxin activity assays can be employed as adjunctive diagnostic tools for discriminating infection as the cause for fever or sepsis presentations (Level 2) [2].

**Table 1: Non-Infectious Causes of Fever**

<b>Hyperthermia Syndrome</b> Environmental (heatstroke) Drug-induced Neuroleptic malignant syndrome Malignant hyperthermia Serotonin syndrome	<b>Intra-abdominal</b> Acalculous cholecystitis Pancreatitis Ischemic bowel Cirrhosis (without primary peritonitis) Hematoma Solid organ injury GI bleed	<b>Hematologic/Immunologic</b> Hematomas Deep vein thrombosis Fat emboli Pulmonary embolus Pulmonary infarct Acute hemorrhage
<b>Neurological</b> Subarachnoid hemorrhage Cerebral infarction Alcohol withdrawal	<b>Immunologic</b> Postoperative fever Transfusion reactions Organ transplant rejection Systemic lupus erythematosus Adult Still's disease Rheumatoid Arthritis	<b>Neoplastic</b> Hodgkin's, non-Hodgkin's lymphoma Leukemia Multiple myeloma Sarcoma Tumors of the liver, brain, kidney, colon, gallbladder and pancreas
<b>Soft tissue</b> Decubitus ulcers		
<b>Vascular</b> Stroke Myocardial infarction Thrombophlebitis	<b>Endocrine</b> Adrenal Crisis Thyrotoxicosis	<b>Renal</b> IV contrast reaction

Adapted from "Potential causes of abnormally elevated body temperatures in the ICU patient" Critical Care Med 2009 Vol. 37, No. 7

### **Blood Cultures**

If clinical evaluation of the patient suggests that the fever is likely infectious in etiology, then blood cultures should be obtained (Level 2) [2]. The sensitivity of blood cultures depends on several factors, the most important being collection prior to antibiotic initiation and volume of blood drawn. It is recommended that 3 to 4 blood cultures be collected within 24 hours of the onset of fever. Two blood cultures should be drawn from peripheral sites, but not via a peripheral line at the time of insertion because of the potential for contamination with the skin's flora. If a central venous catheter is present and considered to be a potential infectious source, at least one blood culture should be drawn from it. Following this, further blood cultures should be obtained based upon clinical judgment rather than routinely with each temperature

elevation (Level 2) [2]. Obtaining blood cultures more than every 24 hours is rarely useful. Additional blood cultures should be drawn thereafter only when there is clinical suspicion of continuing or recurrent infection or to assess antimicrobial response 48–96 hours after initiation of appropriate therapy [2].

### **Intravascular Catheters**

Intravascular catheters are a major source of nosocomial blood stream infections. The highest risk of infection is associated with short term, non-cuffed hemodialysis catheters. In spite of this, intravascular catheters should not be routinely cultured unless a central line-associated bloodstream infection (CLABSI) is suspected. When new onset fever is seen in patients who lack significant risk factors for sepsis (young, immunocompetent, etc.) and who have no other obvious source of infection, it is reasonable to suspect CLABSI. Although absent in most cases, the presence of inflammation (with or without purulence) at the catheter insertion site in patients with signs and symptoms of sepsis, is highly predictive of catheter-related bacteremia. Other findings suggesting that the intravascular catheter is the source of infection include difficulty drawing or infusing through it. Furthermore, catheters that have been in place for less than 3 days are less likely to be infected [2].

The diagnosis of CLABSI is made when a colonized catheter is associated with a contaminant blood stream infection with no other plausible cause. While negative blood cultures from a central line can help to exclude CLABSI, positive blood cultures drawn from the catheter may indicate either infection or colonization. Ideally, quantitative cultures should be used in order to identify the catheter as the source of the infection. If the quantitative culture is drawn through an infected catheter, a ten-fold or greater increase in concentration of organisms will be noted when compared to the blood culture drawn simultaneously from a peripheral vein. Unfortunately, due to their expense, quantitative cultures are not often used. These provide useful information, however, when surgically implanted catheters that cannot be readily removed are the suspected source of infection. An alternative to quantitative cultures with equivalent specificity but lower sensitivity is the method of assessing the differential time to positivity for peripheral vs. catheter blood cultures. In this method, if both sets of cultures are positive for the same organism and the set drawn through the catheter becomes positive at least 120 minutes earlier than the peripheral culture, the diagnosis of CLABSI is made [6]. If there is evidence of a tunnel infection, embolic phenomenon, vascular compromise, or septic shock, the catheter should be removed and a new catheter inserted at a different site (Level 2) [2].

### **Pulmonary Infections**

The presence of respiratory secretions and abnormal chest radiographs are customary in the surgical and trauma ICU setting, but not always representative of respiratory infection. It has been estimated that up to 50% of trauma patients with clinical evidence of pneumonia are undergoing a SIRS response [7]. Clinical parameters for the diagnosis of nosocomial pulmonary infection, such as the Clinical Pulmonary Infection Score (CPIS) and National Nosocomial Infection Surveillance [8] developed by the CDC, provide a scoring system for the diagnosis of ventilatory associated pneumonia (VAP) [9]. Although neither has been shown to consistently predict the incidence of VAP, the CPIS appears to be a superior tool in diagnosing VAP. There is, however, considerable inter-observer variability [10]. A meta-analysis conducted on the diagnostic performance of the CPIS for VAP has concluded that its diagnostic accuracy is moderate, with a sensitivity between 72 and 77% and specificity between 42 and 85% [11]. A prospective observational study on the role of CPIS in the diagnosis of trauma-associated pneumonias (TAP) concluded that CPIS does not reliably predict a positive bronchoalveolar lavage (BAL) at  $10^4$  or  $10^5$  CFU/ml and therefore should not be used to determine the indication for a BAL when VAP is suspected [12].

**Table 2: Clinical Criteria for Pulmonary Infection Diagnosis**

<b>Clinical Pulmonary Infection Score</b>	
<p><b>Temperature</b>                      0 point: <math>\geq 36.5</math> and <math>\leq 38.4</math> °C                      1 point: <math>\geq 38.5</math> and <math>\leq 38.9</math> °C                      2 point s: <math>\geq 39.0</math> or <math>\leq 36.5</math> °C</p> <p><b>Oxygenation (PaO<sub>2</sub>/FiO<sub>2</sub>)</b>                      0 point: PaO<sub>2</sub>/FiO<sub>2</sub> &gt; 240, ARDS, or pulmonary contusion                      2 point s: PaO<sub>2</sub>/FiO<sub>2</sub> &lt; 240 and no evidence of ARDS</p> <p><b>White Blood Cell Count</b>                      0 point: <math>\geq 4,000</math> and <math>\leq 11,000</math>                      1 point: &lt; 4,000 or &gt; 11,000                      2 points: &lt; 4,000 or &gt; 11,000 AND &gt; 500 band forms</p> <p><b>Chest Radiograph</b>                      0 point: No infiltrate                      1 point: Diffuse or patchy infiltrates                      2 points: Localized infiltrate</p> <p><b>Tracheal Secretions</b>                      0 point: None or scant                      1 point: &gt; Non-purulent                      2 points: Purulent sputum</p> <p><b>Culture of tracheal aspirate</b>                      0 pt: Minimal or no growth                      1 pt: Moderate or more growth                      2 pt: Moderate or greater growth</p>	<div style="border: 1px solid black; padding: 5px; display: inline-block;"> <p><b>Total score of &gt; 6 points suggests VAP</b></p> </div>

Adapted from Critical Care 2008; 12(2): R56.

<b>NNIS Pulmonary Infection Criteria</b>	
<p><b>Radiographic Signs</b>                      Two or more serial chest radiographs with at least 1 of the following:</p> <ul style="list-style-type: none"> <li>▪ New or progressive and persistent infiltrate</li> <li>▪ Consolidation</li> <li>▪ Cavitation</li> </ul> <p><b>Microbiological Criteria</b>                      At least one of the following:</p> <ul style="list-style-type: none"> <li>▪ Positive growth in blood culture without another infectious source</li> <li>▪ Positive growth in culture or pleural field</li> <li>▪ Positive quantitative culture from BAL</li> <li>▪ (<math>&gt; 10^4</math>) or protected specimen brushing (<math>&gt; 10^3</math>)</li> <li>▪ <math>\geq 5\%</math> of cells with intracellular bacteria on Gram-stained BAL fluid</li> <li>▪ Histopathological evidence of pneumonia</li> </ul>	<p><b>Clinical Signs</b>                      At least 1 of the following:</p> <ul style="list-style-type: none"> <li>▪ Fever (temperature &gt; 38 C)</li> <li>▪ WBC &lt; 4000 or &gt; 12000 cells/<math>\mu</math>L</li> <li>▪ Altered mental status, for adults <math>\geq 70</math> years, with no other recognized cause</li> </ul> <p>Plus at least 2 of the following:</p> <ul style="list-style-type: none"> <li>▪ New onset of purulent sputum, or change in character of sputum</li> <li>▪ Increased respiratory secretions, or increased suctioning requirements</li> <li>▪ New-onset or worsening cough, or dyspnea, or tachypnea</li> <li>▪ Wales or bronchial sounds</li> <li>▪ Worsening gas exchange</li> <li>▪ Increased oxygen requirements</li> </ul>

Portable chest radiography (CXR), with its high sensitivity but poor specificity, is adequate in the initial evaluation of fever. Preferably, these should be obtained in an erect sitting position. Among all radiographic findings, unilateral air bronchograms have the best predictive value for the diagnosis of pneumonia. Although routinely used, data has shown that even in controlled exposure conditions, more than 30% of the CXR films are considered suboptimal and in many instances correlate poorly with CT

scan findings. Bedside lung ultrasound (US) has been shown to carry a diagnostic accuracy for ARDS comparable to that of bedside radiography and is being increasingly used in ICU patients [13]. According to a prospective study of 42 general ICU patients conducted by Xirouchaki et al, chest US was found to have better diagnostic performance than CXR in the identification of consolidation, interstitial syndrome as well as pleural effusions. This study concluded that bedside US could be used as an alternative to chest CT scans in the ICU setting [9]. CT scans, however, are reasonable in immunocompromised patients in order to rule out opportunistic diseases [2].

Pulmonary secretions should be sent for Gram stain and culture only when a pulmonary infectious source is strongly suspected. However, even in the presence of clinical signs and laboratory values indicative of infection, sputum evaluations might not be high yield. A retrospective study of the relationship between fever, leukocytosis and a positive respiratory culture concluded that no level of fever or range of leukocytosis demonstrated a correlation with positive respiratory cultures. Furthermore, the authors did not recommend obtaining respiratory culture during the initial 14 days of hospitalization based on fever and/or leukocytosis alone in traumatically injured patients [7].

Current literature suggests that expectorated or suctioned specimens are adequate for initial evaluation of pulmonary infections in the non-intubated ICU population (Level 2) [2]. Specimens that demonstrate a preponderance of epithelial cells on initial Gram stain are not suitable and should be discarded. If a diagnosis of pneumonia is not definite based on clinical and radiographic findings, respiratory secretions can be obtained from expectorated sputum, nasotracheal or endotracheal aspirate. Due to concerns of sample contamination and dilution, the use of saline infusion should be avoided unless adequate specimens cannot be otherwise obtained [2].

Intubated patients suspected of pulmonary infection based upon radiographic findings should undergo either bronchoscopically directed aspiration or catheter-directed lavage of pulmonary secretions. Quantitative cultures of such aspirates should be performed to confirm the presence of a clinically significant infection. Quantitative cultures obtained via bronchoalveolar lavage (BAL), protected specimen brush, and tracheobronchial aspirates are equivalent in diagnosing VAP and should be performed in the presence of a discrete lobar infiltrate [1,10]

Due to the need for expeditious identification of the source of infection in an ICU patient, awareness of the reliability of preliminary culture results is of great importance. Two prospective and retrospective studies conducted at Presley Regional Trauma Center assessed the utility of preliminary BAL results in suspected VAP and showed that preliminary BAL results are highly predictive of final culture results. According to this study, preliminary BALs had a positive predictive value of 100%, whereas the negative predictive values of “no growth to date” and insignificant BALs were 99% and 95%, respectively. Although preliminary BALs with significant growth are also highly predictive of VAP, the risk of additional significant isolates appearing on the final BAL culture results precludes the use of these results in the selection of antimicrobial agents [14].

Pleural fluid, identified in up to 62% of ICU patients, is transudative in 50% of cases. Therefore, its culture is not indicated in every febrile patient. Due to low sensitivity and specificity, CXRs are considered unreliable in the identification of pleural effusions in the ICU population. Bedside ultrasonography is an alternative that is highly sensitive and capable of identifying even small effusions (< 5ml) [15]. Furthermore, bedside US has been shown to be superior to CXR and comparable to CT scanning, for the diagnosis of pleural effusions in mechanically ventilated patients [16]. Indications for pleural fluid sampling under US guidance are listed in Table 4. (Level 2) [15]. Pleural fluid obtained via thoracentesis should be sent for Gram stain, culture and cytology. In order to determine if the effusion is exudative or transudative, the pleural fluid's pH, protein, glucose, and lactate dehydrogenase concentration should be obtained as well (Level 2) [15]. The patient's risk for exposure should be used to determine the need for fungal and mycobacterial cultures [2].

**Table 4. Indications for Pleural Fluid Sampling (Level 2) [15]**

<ul style="list-style-type: none"> <li>• Evidence suggestive of infection (otherwise unexplained):             <ul style="list-style-type: none"> <li>○ Ipsilateral pneumonic process</li> <li>○ Fever</li> <li>○ Leukocytosis</li> <li>○ Elevated serum procalcitonin level</li> </ul> </li> <li>• Suspicion of tuberculosis</li> </ul>	<ul style="list-style-type: none"> <li>• Suspicion of malignancy</li> <li>• Persistent or enlarging effusion</li> <li>• Clinical deterioration</li> <li>• Potential for contamination of pleural space:             <ul style="list-style-type: none"> <li>○ Recent thoracic surgery</li> <li>○ Trauma</li> <li>○ Fistula</li> </ul> </li> </ul>
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**Urinary Tract Infections**

A catheter associated urinary tract infection (CAUTI) is defined as signs or symptoms indicative of a urinary tract infection as well as a single catheter specimen or midstream voided urine containing at least 10<sup>3</sup> CFU/mL bacterial species. Although bacteriuria is the most common source of gram-negative bacteremia in hospitalized patients, it accounts for a minority of bacteremias in the ICU setting. In general, bacteriuria and candiduria represent colonization and are rarely the cause of fever in catheterized patients. However, the presence of urinary tract obstruction, recent urologic manipulation or surgery, and granulocytopenia all increase the likelihood that fever is secondary to a CAUTI [2]. The most common signs and symptoms of CAUTI are listed below. In the catheterized patient, the presence or absence of odorous or cloudy urine should not be used to distinguish colonization from infection or to guide diagnostic work up (Level 1) [17].

**Table 5. UTI Signs and Symptoms**

General Patient		Spinal Cord Injury Patient
New onset or worsening fever	Costovertebral angle tenderness	Increased spasticity
Altered mental status	Flank pain	Autonomic dysreflexia
Rigors	Acute hematuria	Sense of unease
Malaise	Pelvic discomfort	
Lethargy		

When an ICU patient develops fever and clinical assessment is suggestive of a UTI, a urine sample should be obtained for culture. A retrospective study looking at 510 surgical ICU patients concluded that fever and/or leukocytosis are not associated with the development of UTI within the first 14 days of admission [18]. It has been suggested that urinalysis and culture are not mandatory during the initial 72 hours postoperatively (unless urological procedure was performed) if fever is the only clinical finding (Level 3) [2].

Urine specimens should be collected by “clean catch” or sampling port if the patient is catheterized and these should be processed in the laboratory within an hour. The sample should never be obtained from the collecting bag (Level 2) [2]. The presence of pyuria and bacterial counts greater than 10<sup>3</sup> CFU/mL does not necessarily prove that the patient’s fever is secondary to a CAUTI. Studies have consistently shown that in most cases it is not the cause of fever (Level 2) [2] [19]. Obtaining Gram stains of the centrifuged sample reliably shows the presence of infecting organisms and can help determine appropriate treatment of catheter-associated urosepsis (Level 2) [2]. The absence of pyuria in a symptomatic patient suggests a diagnosis other than CAUTI (Level 1) [17].

**Wound Evaluation**

Surgical and superficial wounds should be inspected at least once daily for signs of infection as part of the fever evaluation (Level 2) [2]. Drainage emanating from a superficial wound does not require cultures or Gram stain because these can be treated without anti-microbial agents. However, if purulence is expressed from within the tissue it should be opened in order to obtain Gram stain and cultures from deep within the wound site (Level 2) [2]. Tissue biopsies are preferable to superficial cultures obtained with swabs. Superficial cultures of skin overlying a wound should not be performed [2].

## **Sinusitis**

Ventilator associated sinusitis (VAS) is a common cause of fever of unknown origin in critically ill patients. Infectious sinusitis affects 27% of mechanically ventilated patients and is the cause in 25% of fever of unknown origin in the ICU. Furthermore, this review reported that ventilator associated pneumonia was present in 41% of critically ill adults diagnosed with VAS [20]. Sinusitis is most commonly caused by obstruction of the ostia draining the sinuses due to a nasotracheal or nasogastric tube. Clinical findings are not always present in the ICU population, where as little as 25% of those affected will have purulent nasal discharge [2]. Gram-negative bacilli represent 60% of the bacterial isolates in nosocomial sinusitis, with *Pseudomonas aeruginosa* being most common. *Staphylococcus aureus* is the most common gram-positive bacteria, responsible for about one third of cases. If clinical evaluation suggests that sinusitis may be the source of fever, a CT scan of the facial sinuses should be obtained (Level 2). Sinus fluid sampling should be pursued via puncture and aspiration of the involved sinuses if there is no response to empiric therapy. The aspirated fluid should be sent for Gram stain and culture (Level 1) [2].

## **Clostridium difficile and Enteric Pathogens**

*Clostridium difficile* colitis is the most common cause of diarrhea-related fever and should be suspected in any patient with fever, diarrhea, and a history of receiving antibacterial or chemotherapeutic agents within the previous 60 days. Although most ICU patients will present with diarrhea if *C. difficile* is the culprit, postoperative patients may instead present with ileus, toxic megacolon or leukocytosis. Current recommendations suggest that evaluation should be initiated with one stool sample for *C. difficile* common antigen, EIA for toxin A and B, or tissue culture assay. If the first specimen for *C. difficile* is negative and testing is performed by an EIA method, send an additional sample for *C. difficile* EIA evaluation. A second specimen is not necessary if the common antigen test was negative (Level 2) [2].

If severe illness is present and rapid tests for *C. difficile* are negative or unavailable, consider flexible sigmoidoscopy, which is a highly specific test (Level 3). Due to the associated risk of bowel perforation with this invasive procedure, direct visualization of pseudomembranes via endoscopy should be reserved for cases in which laboratory results are not readily available or if there is a high likelihood of having toxin assays with false negative results. Although the use of empiric therapy is not generally recommended if two stool evaluations (using a reliable assay) are negative, consider empiric therapy with vancomycin while awaiting diagnostic studies in the setting of severe illness (Level 2) [2].

Other organisms that can cause fever and diarrhea include *Salmonella*, *Shigella*, *Campylobacter jejuni*, *Aeromonas*, *Yersinia*, *Escherichia coli*, *Entamoeba histolytica*, and multiple viruses. These are typically community-acquired organisms, however, and are unlikely to be the source of fever in an ICU patient unless the patient was immunocompromised or experiencing diarrhea prior to ICU admission. Therefore, sending stools for bacterial cultures or ova and parasite examination should generally be avoided as part of a fever evaluation. These tests should only be done if the host is immunocompromised or meets any of the previously mentioned reasons for increased suspicion (Level 2) [2]. Testing for norovirus is usually performed in outbreak settings and should involve infection control and public health authorities (Level 3) [2].

## **Evaluation of the CNS**

If fever is accompanied by altered consciousness or focal neurologic deficits, lumbar puncture should be obtained, unless contraindicated (Level 3). However if new focal neurologic findings raise suspicion for intracranial disease, an imaging study is usually required before performing a lumbar puncture (Level 2). Cerebrospinal fluid (CSF) should be sent for Gram stain and culture. Further testing for tuberculosis, fungal disease or neoplasm is dependent on the clinical situation (Level 2). In febrile patients with an intracranial device, CSF should be obtained for analysis from the CSF reservoir. If CSF flow to the subarachnoid space is obstructed, it may also be prudent to obtain CSF from the lumbar space (Level 3). In patients with ventriculostomies who develop stupor or signs of meningitis, the catheter should be removed and the tip cultured (Level 3) [2].

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